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Involvement of the locus coeruleus in Pick's disease with or without Pick body formation*

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Summary. Brains affected by the fronto-temporal type of Pick's disease were classified into two subgroups according to whether Pick bodies (PBs) were detectable in cerebral cortex (PB-positive group, six cases) or not (PB-negative group, eight cases), and examined neuropathologically. Controls included seven patients with non-degenerative diseases. The neuronal population in the locus coeruleus (LC) was estimated quantitatively in preparations from the middle part of the LC. The data were analyzed statistically by the Mann-Whitney U-test. Histological and ultrastructural studies were also carried out. The following results were obtained: (1) there were no appreciable differences between the PB-positive and PB-negative groups with regard to age at onset, age at death, duration of illness, clinical stage at death, and brain weight; (2) the mean nerve cell counts in the LC were 43.7 ± 5.2 in the controls, 28.8 ± 11.7 in the PB-positive group, and 42.9 ± 7.6 in the PB-negative group. The nerve cell count in the PB-positive group was significantly lower ($P < 0.05$) than those in the controls and the PB-negative group; and (3) in each of the PB-positive cases, PBs were disclosed in the LC, in medium-sized melanin-laden neurons and small neurons. PBs were globular or lobulated, and their fine structure was identical to that of typical PBs in the cerebral cortex. In conclusion, PB formation may play an important role in neuronal decrease in the LC of PB-positive cases, whereas the LC may not be affected in PB-negative cases. In this respect, Pick's disease with PB formation appears distinct from that without PB formation.

Key words: Pick's disease – Locus coeruleus – Cell counts – Statistical analysis – Pick body

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The locus coeruleus (LC) is said to be vulnerable to various neurodegenerative disease [8]. However, few reports have concerned this nucleus in Pick's disease [4]. Our previous communication focusing on the topography of Pick bodies (PBs) showed that the LC was vulnerable to PB formation [1]. In the present study cases of Pick's disease were divided into two subgroups and the neuronal population in the LC was assessed and compared in each subgroup. This is the first systematic study to investigate the relationship between neuronal loss and PB formation in LC.

Materials and methods

Fourteen cases of Pick's disease, which were well documented clinically and neuropathologically, were selected for study. The clinical stage at death was assigned on the basis of C. Schneider's classification [7]. Atrophy was circumscribed on the frontal, temporal, and insular lobes in each case, with occasional extension to the inferior parietal lobulus (case 13). Cases were divided into two subgroups on the basis of whether PBs were present or absent in cerebral cortex: the PB-positive group, six cases, and the PB-negative group, eight cases, respectively. In each case, PBs in the cerebral cortex, including the hippocampal formation, were identified under the electron microscope and reported in our previous communication [1]. Controls included seven patients with non-degenerative diseases, as assessed by clinical and neuropathological examinations. The clinical data and brain weight of each case are summarized in Table 1.

In each case, a cross-section was taken through the middle part of the upper pons (Fig. 1), at the center of the LC, and embedded in paraffin. The 4-μm-thick sections were stained with hematoxylin and eosin (H&E) and by Bodian's method for light microscopy. In the LC, both melanin-laden medium-sized neuronal cells and melanin-free small cells with visible nuclei were counted on both sides under the light microscope using the H&E preparations. The mean cell counts of each case were estimated for analysis (Table 1). In addition, histological examination was carried out on Bodian's and H&E preparations. Formalin-stocked tissues of four cases in the PB-positive group (cases 3–6) were processed by the conventional method for electron microscopy. PBs and Lewy bodies were observed ultrastructurally.

Table 1. Summary of patients and results

Patient no.	Sex	Onset/death (years)	Duration (years)	Clin. stage at death	Brain weight (g)	Cell count	PBs in LC	PB-bearing cell count
Pick's disease, PB-positive group								
1	M	45/54	10	2	1290	51	G&L	7
2	F	56/65	10	2	1080	26	G&L	13
3	M	50/63	13	3	1100	21	G	2
4	F	60/69	10	3	1020	30	G&L	2
5	M	64/74	10	3	950	27	G&L	8
6	F	57/71	15	3	820	18	G&L	4
Pick's disease, PB-negative group								
7	M	68/70	2	2	1180	28	–	
8	M	50/62	12	2	1100	49[a]	–	
9	M	55/66	11	2	1050	49	–	
10	F	59/66	7	2	980	44	–	
11	F	57/61	4	3	–	49	–	
12	F	52/68	17	3	990	35	–	
13	M	51/57	7	3	940	46	–	
14	F	55/65	10	3	820	43	–	
Controls, patients with non-degenerative diseases								
15	F	/59			1340	41	–	
16	F	/60			1370	50	–	
17	F	/62			1140	49	–	
18	M	/65			1290	42	–	
19	M	/70			1280	48	–	
20	M	/73			1140	39	–	
21	M	/75			1280	37	–	

Pick body (PB)-positive group: Cases of Pick's disease with PB formation in the cerebral cortex; PB-negative group: cases of Pick's disease with no PB formation in the cerebral cortex
Clinical stage at death was based on C. Schneider's classification [7]
Cell count: Mean cell count in both sides in a 4-μm-section; a: only one side (right) was available for examination; PB in LC: PBs in the locus coeruleus; G: globular PBs; L: lobulated PBs; PB-bearing cell count: mean of PB-bearing cell counts on both sides in a 4-μm-section

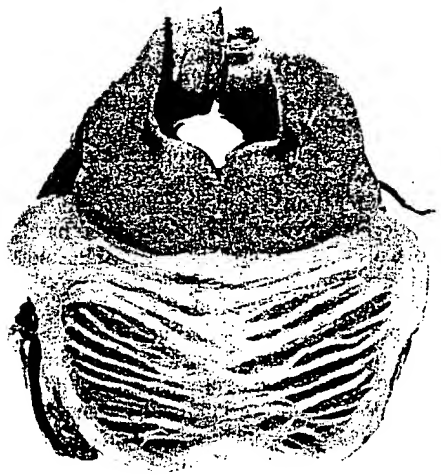

Fig. 1. Cross-section through the middle part of the upper pons, at the center of the locus coeruleus (LC). Case 14, a PB-negative case

The Mann-Whitney U-test was performed for all the variables described in Table 1. The criterion for statistical significance was the 0.05 level.

Results

Statistical analysis

Clinical factors. There was no statistically significant difference in age at death between the controls (mean, 66.3 ± 6.4 years), the PB-positive group (mean, 66.0 ± 7.1) and the PB-negative group (mean, 64.4 ± 4.2). In addition, no significant differences between the PB-positive and PB-negative groups were observed for the following factors: age at onset (mean, 55.3 ± 6.9 years for the PB-positive and 55.9 ± 5.8 for the PB-negative groups); age at death; duration of illness (mean, 11.3 ± 2.2 years for the PB-positive and 8.8 ± 4.8 for the PB-negative groups); and clinical stage at death.

Brain weight. As compared with controls (mean, 1262.9 ± 90.3 g), a significantly lower brain weight

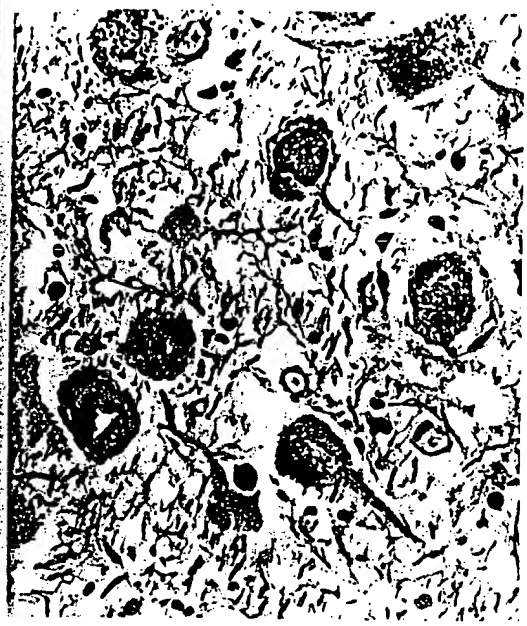

Fig. 2. Pick bodies (PBs) were globular or lobulated in the LC. Case 1, Bodian stain, × 340

was observed in the PB-positive group (mean, 1043.3 ± 157.8 g, $P < 0.025$) and the PB-negative group (mean, 1008.6 ± 116.1 g, $P < 0.01$), but there was no difference between the PB-positive and PB-negative groups.

Cell counts in LC. The nerve cell count in the LC of the PB-positive group (mean, 28.8 ± 11.7) was significantly lower ($P < 0.05$) than that in the controls (mean, 43.7 ± 5.2) and the PB-negative group (mean, 42.9 ± 7.6), but there was no difference between the controls and the PB-negative group.

Histopathology and ultrastructure

In all cases in the PB-positive group in which PB formation was observed in the cerebral cortex, PBs were detected frequently in medium-sized melanin-laden neurons but seldom in small neurons of the LC. Typical PBs with a globular structure were found in the LC; however, PBs were lobulated in five of six cases (Fig. 2). With regard to PB formation and the neuronal population, a correlation might exist between total cell count and PB-bearing cell count.

Under the electron microscope, PBs with globular and lobulated structures (Fig. 3a, b) were identical to those observed in the cerebral cortex: they were composed of random aggregations of tubular structures, which were smooth in their outer surface, as described by Oyanagi [6]. Case 4 showed scattered Lewy bodies whose fine structure was in keeping with that of previous observations. These were attributed to age-related senile changes. Alzheimer's neurofibrillary changes were not detected in this series.

Discussion

No appreciable neuronal decrease was found in the LC in the PB-negative group as compared with controls. The pathological process in the PB-negative group was, thus, concluded not to cause neuronal loss in this nucleus.

Statistical analysis disclosed that the neuronal population in the LC was significantly lower in the PB-positive group than in the PB-negative group and the controls. There were no differences in clinical factors or brain weight between the PB-positive and PB-negative groups. Therefore, the decrease in the neuronal population might be due to a degenerative process in the PB-positive group. Since PB-bearing neurons were a constant finding in the LC in this group, PB formation may play a role in neuronal loss, as discussed in our previous communication on the cerebral cortex [2].

In an examination of three cases of Pick's disease with typical PBs, Forno et al. [4] pointed out that perikaryal inclusions were often multiple and were found in all three cases, a finding that is in good agreement with the present study. However, they reported that no obvious nerve cell loss was present in the LC, which is in conflict with the present findings.

In conclusion, in the fronto-temporal type of Pick's disease, in which PBs were found in cerebral cortex, PBs were always found in the LC accompanied with neuronal loss. On the other hand, when PBs are not detected in cerebral cortex, the LC may not be affected. In terms of the adrenergic and sleep-regulating functions that the LC shares, the lesion should be manifested in the clinical symptoms, but this remains to be elucidated.

Pick's disease is characterized by circumscribed atrophy in both cerebral hemispheres and, indeed, the neuropathological diagnosis does not depend on the presence of PBs. Constantinidis et al. [3], however, have claimed that Pick's disease should be divided into two subgroups depending on whether or not PBs and/or neuronal swelling are present, because of the differences in the topography of the cerebral lesions and associated clinical symptoms. Recently, from the immunocytochemical standpoint, Murayama et al. [5] argued that the group without PBs and swollen chromatolytic neurons should be excluded from Pick's disease. In previous reports from our laboratory [1, 2], PBs were found to be distributed constantly in selected

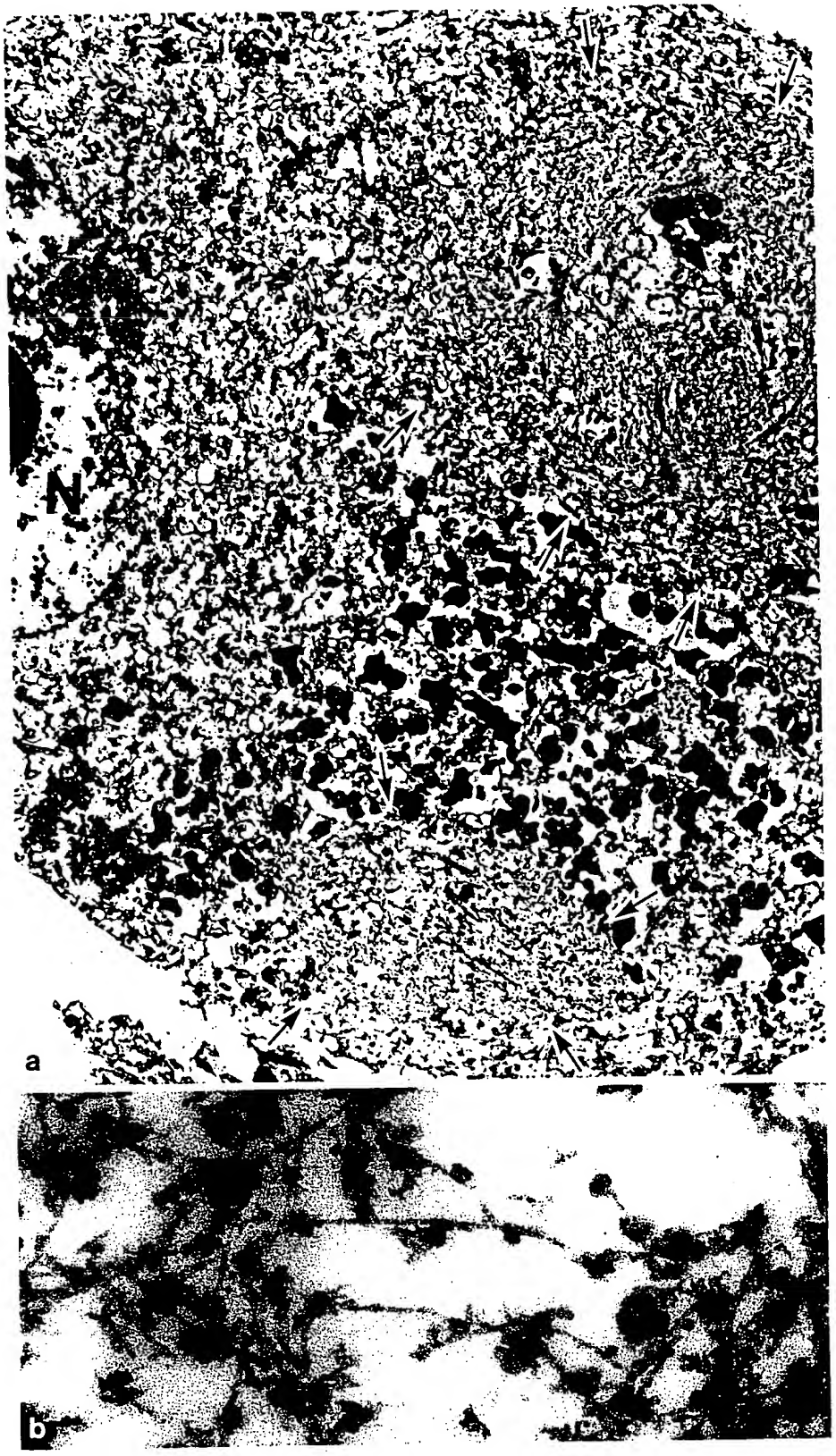

Fig. 3. a Ultrastructure of a lobulated PB. The PB was composed of randomly arranged tubular structures. Case 6, × 4300. b High-power view of a. The tubular structures were about 15 nm in diameter and smooth in their outer surface, without side arms or fine granules attached on their outer surface. × 66000

nuclei throughout the central nervous system. This study provides additional justification for the neuropathological distinction of Pick's disease with PB formation from that without PB formation. On this basis, the authors consider that Pick's disease should be divided into two subgroups according to the presence or absence of PBs.

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